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REPROGRAMMING IMMUNE CELLS TO DEVELOP ALLOGENIC CAR CELL-BASED THERAPIES

Keywords: CAR NK cells, CAR T cells, CAR, CD3ζ/CD247, therapy

INVENTION NOVELTY

The invention comprises an optimized CRISPR-Cas9-mediated gene transfer for efficient integration of novel truncated chimeric antigen receptors (CARs) into the CD3ζ/CD247 locus of human T or natural killer (NK) cells. Resulting T or NK cell populations lack the expression of endogenous T cell receptors (TCRs). TCR complex-deficient lymphocytes provide the basis to develop "off-the-shelf" allogenic CAR cell products for novel strategies to treat cancer, autoimmune diseases, and graft versus host disease (GvHD).

VALUE PROPOSITION

CAR cell-based therapies rely on reprogramming cell specificity and modulating their immune cell function. The proposed technology overcomes critical technical challenges in the production of therapeutic cell products: (i) The gene transfer is performed by electroporation of the CRISPR-Cas9 machinery. In addition, the protocol can be adapted to all other CRISPR-Cas systems, TALENs and other highly specific nucleases. The reduced size of the truncated CAR construct improves gene transfer capacity to co-deliver other functional cargo, such as cytokine support systems. (ii) All lymphocytes that express the CD247 gene including Tregs, natural killer cells (NKs) and unconventional T cells can also be reprogrammed paving the way for the development of new, innovative CAR cell products. (iii) CD3ζ- KI CAR NK cells display higher cytotoxic activity than CAR NK cells, suggesting superior functionality of physiologically regulated CAR expression in NK cells. Primary NK cells with edited CD247 retain missing-self activation and antibody-mediated cytotoxicity, highlighting its potential to create powerful CAR NK cell products.

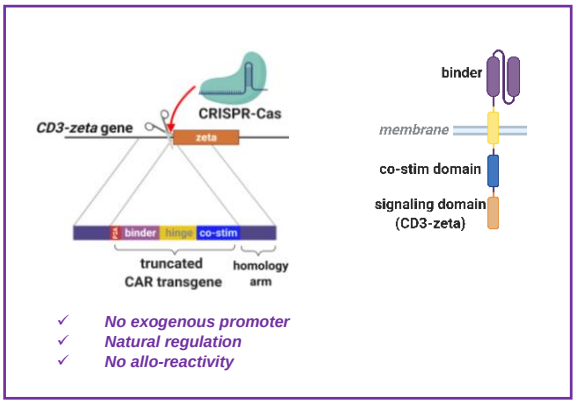

Abb.: Novel CD3-zeta gene editing strategy enables redirection of T cells and NK cells with chimeric antigen receptors (D. Wagner)

TECHNOLOGY DESCRIPTION

The technology is based on targeted CRISPR-Cas9-mediated insertion of a novel truncated CAR construct, which lacks the intracellular CD3ζ signaling domain, into the exon 2 locus of the CD3ζ/CD247 gene of lymphocytes such as T cells. The resulting gene-edited CD247 locus then encodes a CAR-CD3ζ fusion receptor under the control of the endogenous CD3ζ promoter with concomitant loss of endogenous CD3ζ expression. This leads to the suppression of the TCR α/β–subunits, resulting in TCR negative T-cells. Moreover, in contrast to viral transduction or transposon-based gene transfer, genome editing through CRISPR-Cas enables the controlled insertion of the CAR-CD3ζ KI construct into the “natural” genetic context of the CD247 gene. Thus, the proposed, highly versatile technology provides a new genetic method to produce CAR-expressing T or NK cells with an improved safety profile, optimized expression, and increased effectiveness.

COMMERCIAL OPPORTUNITY

In-licensing or collaboration for further development

DEVELOPMENT STATUS

In vitro proof of concept. Further studies on-going to validate the technology; planning of a phase 1 study.

PATENT SITUATION

EP4019538A1, WO2022136551A1

FURTHER READING

Wagner, D. L. et al. (2021) Immunogenicity of CAR T cells in cancer therapy. Nat. Rev. Clin. Oncol. 1–15.

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